Award Number: W81XWH-06-1-0570

TITLE: Poloamer 188 as an Adjunct in Prolonged Hypotensive Resucitation

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REPORT DATE: July 2007

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-07-2007	Annual	1 Jul 2006 – 30 Jun 2007

4. TITLE AND SUBTITLE

Poloamer 188 as an Adjunct in Prolonged Hypotensive Resucitation

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-06-1-0570

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Despite tremendous efforts, exsanguinations remains a leading cause of deaths (approximately 40 %) in both civilian and military trauma. A subset of injured soldiers develop decompensated shock that requires early interventions if they are to survive. This project is testing the ability of a new drug, purified poloxamer 188 (P188), to increase survival and reduce inflammation and organ injury resulting from prolonged periods of hypotensive resuscitation in a model specified by the ARMY. The results are strongly positive. Addition of P188 to standard therapy with Hextend significantly improved survival (p=0.002) and reduced fluid requirements (p=0.0002) in rats subjected to prolonged hypotensive resuscitation. These studies are being followed up with studies with more complex injuries and with uncontrolled hemorrhage in rats, rabbits and pigs.

15. SUBJECT TERMS
Hemorrhagic shock, resuscitation, Poloxamer, drug, survival, inflammation

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	7	19b. TELEPHONE NUMBER *(include area code)*

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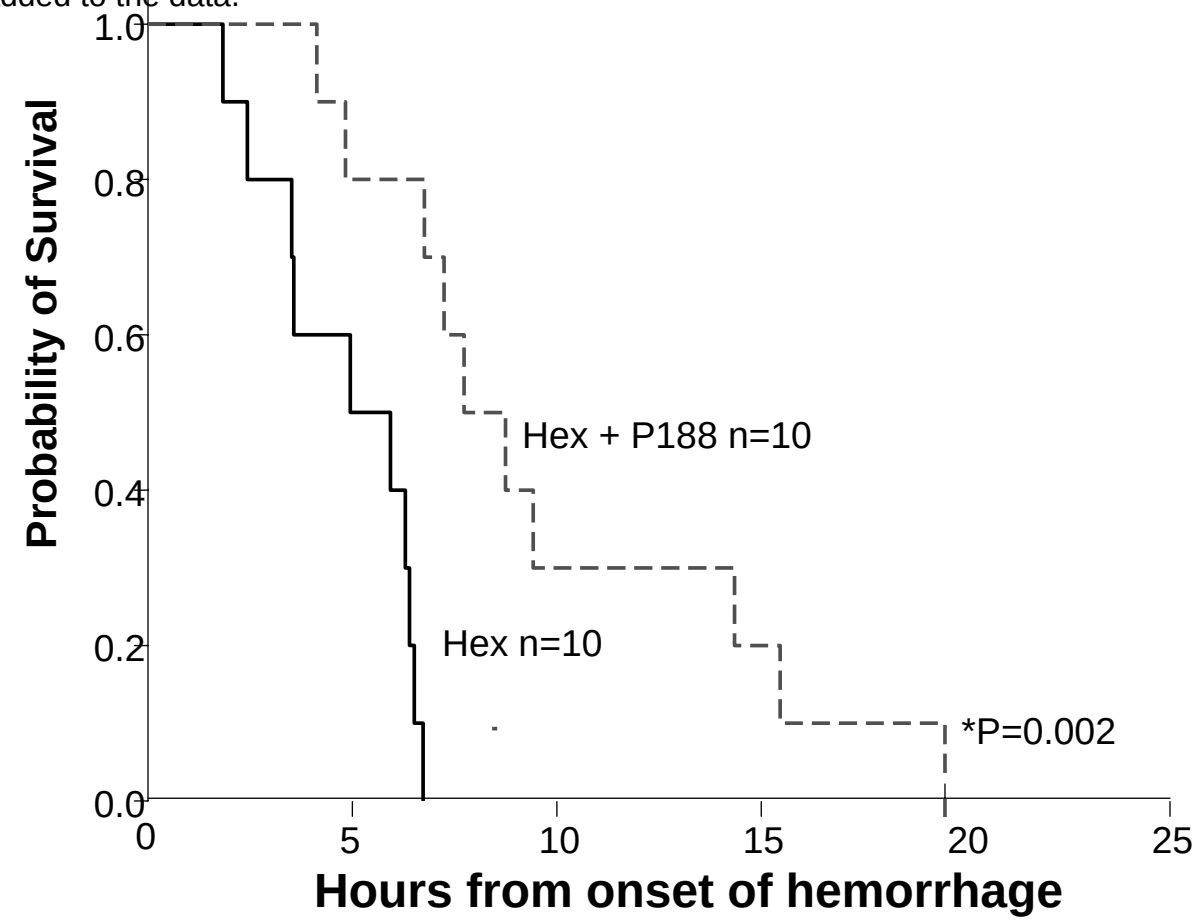
Introduction: This is a report for the first year of a two year project aimed at assessing the potential of purified Poloxamer 188 (P188) as an adjuvant in prolonged hypertensive resuscitation. Numerous pitfalls have been navigated to produce highly significant results that confirm or exceed our initial expectations.

Body:

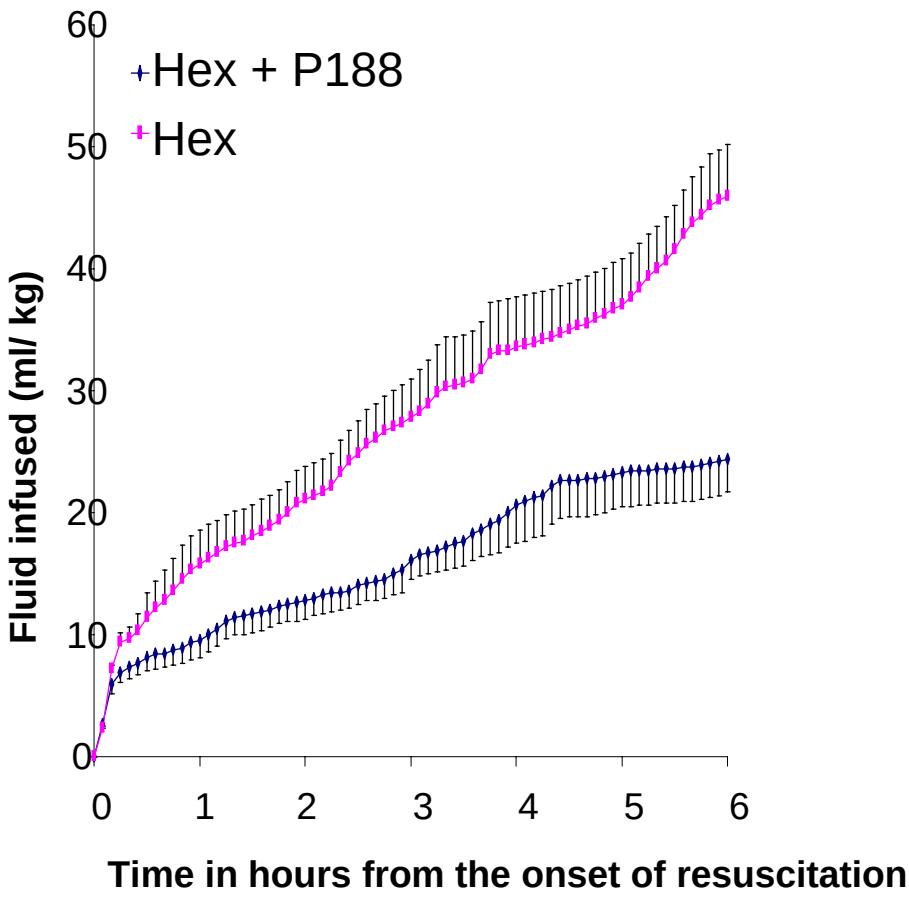
Hypothesis: P188 will improve early survival as well as reduce inflammation and organ injury after prolonged hypotensive resuscitation of lethal traumatic shock.

Experimental Design: Sprague Dawley rats 250-300 gm were bled to BP 30 mm/Hg for 30 min under computer control. They were then infused with Hextend or Hextend plus P188 (~140mg/kg) to BP 60. Additional Hexted or Hextend pluys P188 was infused to maintain BP=60 untill animals decompensated and died. Continuous monitoring of mean blood pressure (MBP), blood loss, volume infusion and heart rate added to the data.



Survival analysis demonstrated a highly significant improvement associated with infusion of P188. There seemed to be two groups of rats. About 70% experienced a 3 hour increase in survival and 30% more than 8 hour increase. This appears to be due to the ability of some rats infused with P188 to maintain BP in the presence of hypovolemia better than others. This is being investigated further.

Fluid Requirements During Hypotensive Resuscitation



A notable and highly significant effect of P188 is that it reduced fluid requirements to maintain BP= 60 during hypotensive resuscitation. This is consistent with the hypothesis that it protected endothelial integrity and prevented fluid leakage into extra vascular spaces. The points are the mean +/- SD for groups of 10 rats.

Effect of P188 on Hypotensive Resuscitation with Hextend

Data and statistical analysis

Group	Hex	Hex + P188	*p* (t-test)
Number of animals	10	10	
Animal Weight (g)	265.60±4.41	269.80±3.87	0.46
Shed Blood to BP 30mmHg (% Total volume)	64.95±2.88%	61.14±2.29 %	0.29
Decompensate timing (min)	13.13±2.17	10.27±2.45	0.37
Fluid requirement to maintain BP at 30mmHg	5.91±1.23	3.86±0.93	0.18
Initial Resus volume to BP 60mmHg (ml/kg)	8.87±0.64	7.01±1.00	0.11
Initial P188 resus to BP 60mmHg (mg/kg)		142.55±20.51	
Resus volume within 1st six hours to maintain BP at 60mmHg (ml/kg/h)	7.66±0.70	4.66±0.44	0.0002
P188 resus within 1st six hours to maintain BP at 60mmHg (mg/kg/h)		81.28±8.29	
Total Resus volume till death (ml/kg/h)	11.17±1.37	4.72±0.81	0.0005
Total P188 resus till death (mg/kg/h)		94.50±16.28	
Survival timing from onset of hemorrhage (min)	288.95±36.70	589.32±99.97	0.002*

*Cal by Gehan-Breslow test

Significant improvement in survival and fluid requirements was produced by P188 in this study. The other paramaters demonstrate that the groups were comparable.

Summary and Conclusions

Controlled Hemorrhage in Awake Rat

1. The Army's computer controlled procedures for controlling hemorrhagic shock work well.
2. P188 improves survival in this model (p=0.002).
3. P188 reduces the volume of fluid required to maintain BP=60 (p=0.0002).
4. P188 + Hextend enables > 8 hour increased survival during hypotensive resuscitation in 30% of animals.
5. Infusion of Hextend with P188 to BP = 60 produces higher more sustained increase in BP than Hextend alone.
6. Some animals increase BP to ~ 80 when infusion stops at BP=60. These animals survive longer, especially with with P188.

Key Research Accomplishments

1) Significant obstacles were overcome in the processes and regulatory procedures of both the military and university.
2) We worked collaboratively with Drs. Pearce and Dlbo at the Walter Reed (WRAIR) to adapt their computer driven model of hemorrhagic shock in rats for use in this project. This required multiple trips and a prolonged stay in Washington but was successful.
3) The model of prolonged hypertensive resuscitation in rats was developed as planned. It took approximately 50 animals to develop procedures and skills to produce consistent reliable results.
4) Addition of Poloxamer 188 to hextend in the standard hypertensive resuscitation protocol produced rather dramatic improvement end results evidence by growing life from six to nine hours, reducing the amount of fluids required. At six hours, 70 percent of the treated animals remained alive while 100 percent of the control had expired.
5) Studies with superior mesenteric occlusion model demonstrated that Poloxamer 188 is a high significant anti-inflammatory cytoprotective effect during ischemia reperfusion.

Reportable Outcomes: Poloxamer 188 continues to meet or exceed our expectations development as an adjuvant to prolong hypertensive resuscitations.

Conclusion: While much remains to be done, available evidence suggests that this can be developed into a valuable agent for use in both military and civilian trauma.

References: None

Appendices: None